REMARKS

Status of the Application, Amendments and Claims

Applicants note that in response to the reply to the Restriction Requirement filed by Applicants on October 14, 2005, the Examiner states that Claims 3-13, 15-33, 35, 52, 62 and 66-83 are withdrawn as being drawn to non-elected inventions (see page 2 of the Office Action). However Applicants note that Claim 62 should not be withdrawn. Claim 62 is drawn to the elected invention. Thus, Claims 1, 2, 14, 34, 36-51, 53-61 and 62-65 are under examination. Confirmation of the status of the claims is requested in the next Communication from the Office.

Amendments to the Claims

Claims 14, 44 and 59 have been canceled.

Claims 1, 34, 38, 48, 51, 55, 63 and 65 have been amended.

New Claims 84-92 have been added.

Claim 1 has been amended to be directed specifically to administration of an inhibitor of TNF-α synthesis and to delete non-elected subject matter. Claims 38, 48, 51, 55, 63 and 65, which are dependent on Claim 1, have been amended to delete non-elected subject matter and to be consistent with Claim 1. Support for these amendments is found in the specification, for example, page 14, line 29 to page 15, line 4 and Claim 1 as originally-filed.

Claim 1 has been further amended to recite "such that the inflamed orthopedic joint is treated." Support for this amendment is found in the specification, for example, at page 11, line 23 to page 12, line 14.

Claim 34, as amended, recites "the method of claim 1, wherein the formulation further comprises at least one growth factor." Support for this amendment is found in the specification, for example, at page 32, line 11 to page 33, line 2.

New Claim 84 is directed to "a method of treating an inflamed orthopedic joint, wherein inflammation of the orthopedic joint results in ankylosing spondylitis, said joint comprising i) opposing hyaline cartilage articular surfaces, ii) a peripheral collagenous capsule defining a central joint space and iii) synovial fluid contained within the joint space, comprising trans-capsularly administering into the joint space a formulation comprising an effective amount of an

inhibitor of TNF-α synthesis such that an inflamed joint is treated." Support for this amendment is found in the specification, for example, at page 19, line 25 to page 20, line 3, and originally-filed Claim 1.

New Claim 85 is directed to "the method of Claim 84, wherein said inhibitor of TNF-α synthesis is infliximab." New Claim 86 is directed to "the method of Claim 84, wherein said inhibitor of TNF-α synthesis is adalimulab." New Claim 87 is directed to "the method of Claim 84, wherein said inhibitor of TNF-α synthesis is CDP-571." New Claim 88 is directed to "the method of Claim 84, wherein said inhibitor of TNF-α synthesis is CDP-870." New Claim 89 is directed to "the method of Claim 1, wherein said inhibitor of TNF-α synthesis is a monoclonal antibody." New Claim 90 is directed to "the method of Claim 1, wherein said inhibitor of TNF-α synthesis is not thalidomide." Support for this amendment is found in the specification, for example, at page 15, line 5 to page 18, line 2.

New Claim 91 is directed to "the method of Claim 49, wherein the growth factor is a bone morphogenetic protein." New Claim 92 is directed to "the method of Claim 49, wherein the growth factor is a growth differentiation factor." Support for this amendment is found in the specification, for example, at page 32, lines 11-26.

No new matter has been added by these amendments. Therefore, entry of the amendments into the application is respectfully requested.

Objections to Claims 1, 2, 14, 34, 36-51, 53-61 and 63-65

A. Claims 1, 2, 14, 34, 36-51, 53-61 and 63-65

Claims 1, 2, 14, 34, 36-51, 53-61 and 63-65 have been objected to as encompassing non-elected inventions.

Applicants have canceled Claims 14, 44 and 59. Applicants have amended independent Claims 1, 38, 48, 51, 55, 63 and 65 have been amended to recite "inhibitor of TNF-α synthesis." Claims 2, 36-37, 39-47, 49-50, 53-54, and 56-62 depend from these claims, and, therefore contain the same limitation. Claim 34, as amended, recites "at least one growth factor." Reconsideration and withdrawal of the objection are respectfully requested.

B. Claim 59

Claim 59 has been objected to as being a duplicate of Claim 38.

Applicants have canceled Claim 59, thereby obviating the objection.

Rejection to Claims 1, 2, 14, 34, 36-51, 53-61 and 63-65 Under 35 U.S.C. § 112, second paragraph

Claims 1, 2, 14, 34, 36-51, 53-61 and 63-65 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1, 2, 14, 34, 36-51, 53-61 and 63-65

The Examiner states that "the method step does not match the goal set forth in the preamble...."

Claim 1 has been amended to recite "such that the inflamed orthopedic joint is treated", as suggested by the Examiner, thereby obviating the rejection. Claims 2, 34, 36-43, 45-51, 53-58, 60, 61 and 63-65 depend from Claim 1, and, therefore, contain the same limitation. Claims 14, 44 and 59 have been canceled.

Reconsideration and withdrawal of the rejection are respectfully requested.

B. Claim 1

The Examiner states that the terms "effective amount" and "high specificity antagonist (HAS)" are relative terms which make the claim indefinite.

Claim 1 has been amended, and no longer recites "high specificity antagonist," thereby obviating the rejection.

In regard to "effective amount", one of ordinary skill in the art of treatment of inflamed joints would understand what is meant by an effective amount of the administered compound, particularly since the claim has been amended to indicate that the effective amount is administered such that the inflamed joint is treated. Further, the specification provides guidance on dosing of an inhibitor of TNF-α synthesis. (see, for example, the specification at page 22, line 10 to page 23, line 21).

Reconsideration and withdrawal of the rejection are respectfully requested.

C. Claims 38, 48 and 59

The Examiner states that "[i]n the absence of a specific recited structure, the recitation of a specific dosage is meaningless."

The definiteness requirement of 35 U.S.C. § 112, second paragraph requires that the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant. See MPEP 2171. Further, "[t]he Examiner's focus during examination of the claims for compliance with the requirement for definiteness of 35 U.S.C. 112, second paragraph, is whether the claim meets the threshold requirements of clarity and precision...." See MPEP 2173.02.

> When the Examiner is satisfied that patentable subject matter is disclosed, and it is apparent to the examiner that the claims are directed to such patentable subject matter, he or she should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness. Some latitude in the manner of expression and the manner of terms should be permitted even though the claim language is not as precise as the examiner might desire.

Id. (emphasis in original)

Applicants have canceled Claim 59 as it is a duplicate of Claim 38. Applicants have amended Claims 38 and 48 to recite administration of "an inhibitor of TNF-α synthesis," rather than a high specificity antagonist. The claims, as amended, "define the patentable subject matter with reasonable degree of particularity and distinctness." Definiteness of claim language must be analyzed, not in a vacuum, but in light of the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. *Id.* One of ordinary skill in the art should understand how to determine and administer how to determine dosages of such inhibitors in units such as "mg/ml" and of "mg". It would be very straightforward for one of ordinary skill in the art to understand what is meant by an inhibitor of TNF-α synthesis "present in the formulation in an amount of at least 100 mg/ml" and "present in the formulation in a maximum amount of 0.5 mg." (see, for example, the specification at page 22, line 10 to page 23, line 21). The claim "apprises one of ordinary skill in the art of its scope and, therefore, serves its notice function.... *Id.* Thus, the claims are clear and precise are definite.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection to Claims 38, 44, 46, 48 and 59 Under 35 U.S.C. § 112, first paragraph

Claims 38, 44, 46, 48 and 59 have been rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement.

A. Claims 44 and 46

The Examiner states that he specification provides no guidance and/or direction or working examples of a sustained release device "which could deliver a formulation comprising an effective amount of an inhibitor of TNF-α synthesis wherein the sustained release device comprises a biosensor...." Further, the Examiner states that "LaVan *et al.* teach that 'no fully automatic long-term *in vivo* system has been brought to market because of stability problems with *in vivo* glucose sensors.'"

While Applicants disagree with the Examiner's position and reserve their rights to file continuing or divisional applications to pursue these claims, in order to expedite prosecution, Applicants have canceled Claim 44.

In regard to Claim 46, Applicants respectfully disagree. Claim 46 recites "wherein the sustained release device comprises an inflammatory-responsive delivery system." Although LaVan *et al.* discloses that there are stability problems with *in vivo* glucose sensors, LaVan *et al.* does not disclose any such problems with a sustained release device that comprises an inflammatory-responsive delivery system. Further, Pike *et al.* (US Publication No. 20030134792, published July 17, 2003), which is cited by the Examiner in a §103(a) rejection, states at paragraph 0053 that a sustained release device comprising inflammatory-responsive delivery systems is "well known in the art," and can be used to administer a therapeutically effective dose of an agent directly at the site. Thus, Claim 46 is enabled.

Reconsideration and withdrawal of the rejection are respectfully requested.

B. Claims 38, 48 and 59

The Examiner states that "[i]n the absence of a specific recited structure the skilled artisan is unable to make the recited compound."

Applicants have canceled Claim 59. Applicants have amended Claims 38 and 48 to recite that the high specificity antagonist is an inhibitor of TNF-α synthesis. One of skill in the art of inflamed orthopedic joint treatment could easily determine how to measure an inhibitor of TNF-α synthesis in a formulation in an amount of at least 100 mg/ml or in a formulation in a maximum amount of 0.5 mg without undue experimentation. (see, for example, the specification at page 22, line 10 to page 23, line 21). Thus, particularly since Applicants have amended these claims to recite an inhibitor of TNF-α synthesis, the rejection is obviated.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection to Claims 1, 2, 14, 34, 37, 47, 49, 51, 54 and 56 Under 35 U.S.C. § 103(a)

Claims 1, 2, 14, 34, 37, 47, 49, 51, 54 and 56 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Lehman *et al.*, "Thalidomide Therapy for Recalcitrant Systemic Onset Juvenile Rheumatoid Arthritis," *The Journal of Pediatrics, 140*:125-127 (2002)) in view of Dunn (EP 1 153 606, published May 10, 2001). The Examiner states that "[i]t would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the formulation comprising thalidomide taught by Lehman *et al.* using the administration route taught by Dunn."

Applicants respectfully disagree. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in some knowledge generally available in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art and not based in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), M.P.E.P. 706.02(j). A prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984), MPEP 2142.02 (VI).

While Applicants disagree with the Examiner's position and reserve their rights to file continuing or divisional applications to pursue these claims, in order to expedite prosecution,

Applicants have amended Claim 1 to recite that the high specificity cytokine antagonist is an inhibitor of TNF-α synthesis. Claims 2, 34, 37, 47, 49, 51, 54 and 56 depend upon Claim 1, and, therefore, contain the same limitation. Applicants have canceled Claim 14. Thus, as amended, Applicants' invention is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering into the joint space an inhibitor of TNF-α synthesis. As taught in Applicants' specification, direct administration of the inhibitor of TNF-α synthesis trans-capsularly is advantageous over systemic treatment. Such advantages include, for example, arresting the inflammation process begun within the joint and the degeneration of the hyaline cartilage, preventing intracapsular nerve irritation, increasing the half life of the inhibitor of TNF-α synthesis in the capsule and reducing unwanted side effects. (see the specification, for example at page 8, line 10 to page 10, line 5).

Lehman *et al.* teaches that two children with systemic onset juvenile rheumatoid arthritis were systemically treated with etanercept (ENBREL®) and thalidomide. Treatment with etanercept was unsuccessful. The treatment with thalidomide demonstrated improvements in arthritis manifestations and laboratory parameters. However, Lehman *et al.* teaches that thalidomide has been shown to have both stimulatory and inhibitory effects on TNF-α activity, and notes that it may increase TNF-α production under some circumstances (see Lehman *et al.* at page 126, column 3). In fact, Lehman *et al.* cites reference number fourteen (14), Gori *et al.*, "Tumor Necrosis Factor-α Increased Production During Thalidomide Treatment in Patients with Tuberculosis and Human Immunodeficiency Virus Coinfection", *J. Infect. Dis. 182*:639-640 (2000) (Exhibit A). Gori *et al.* teaches that thalidomide does not reduce TNF-α levels. In fact, Gori *et al.* reported a progressive increase in TNF-α production following thalidomide treatment. Thus, thalidomide is not an inhibitor of TNF-α synthesis, as recited in the claims. Further, Gori *et al.* states that, in light of these results, they suggest "extreme caution" in undertaking studies that support clinical use of thalidomide.

Therefore, Lehman *et al.* does not teach or suggest administration via trans-capsular injection. Further, Lehman *et al.* does not teach or suggest treating an inflamed orthopedic joint with an inhibitor of TNF-α synthesis. In fact, Lehman *et al.* teaches away from administration of an inhibitor of TNF-α synthesis in favor of a substance known to have at least some stimulatory effects on TNF-α activity (thalidomide). Thus, Lehman *et al.* does not describe or suggest

Applicants' invention, and does not provide a reasonable expectation of successfully treating an inflamed orthopedic joint by trans-capsularly administering into the joint space an inhibitor of TNF-α synthesis.

Dunn teaches treating an inflamed joint by injecting growth hormone and buffer solution into the joint space. (See Dunn, column 7, paragraph 0027). According to Dunn, the hormone is injected into the joint space and not directly into the bone, and in this manner it can be absorbed into the blood stream. Dunn further discloses that anti-cytokines including ENBREL® can be injected prior to, or simultaneously with, the step of injecting a growth hormone and buffer solution into the joint space. (See Dunn abstract and column 8, paragraph 0030; column 9, paragraph 0031). However, although ENBREL® binds soluble TNFα, it does not inhibit TNF-α synthesis. Thus, Dunn does not describe or suggest administration of an inhibitor of TNF-α synthesis.

One of ordinary skill in the art would not be motivated to combine the teachings of Lehman *et al.* and Dunn with any reasonable expectation of success in treating an inflamed orthopedic joint with an inhibitor of TNF-α synthesis, as claimed by Applicants. None of the Examiner's cited references alone or in combination teach or suggest the claimed invention.

In view of the above, Applicants' claims meet the requirements of 35 U.S.C. § 103(a). Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection to Claims 36, 39-43, 45, 58, 60, 61 and 63-65 Under 35 U.S.C. § 103(a)

Claims 36, 39-43, 45, 58, 60, 61 and 63-65 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Lehman *et al.*, "Thalidomide Therapy for Recalcitrant Systemic Onset Juvenile Rheumatoid Arthritis," *The Journal of Pediatrics, 140*:125-127 (2002) in view of Pike *et al.* (US Publication No. 20030134792, published July 17, 2003). The Examiner states that "[i]t would have been obvious to the person or ordinary skill in the art at the time the invention was made to modify the formulation comprising thalidomide, an inhibitor of the production of the cytokine TNF-α, as taught by Lehman, by using the delivery systems disclosed by Pike et al."

Applicants respectfully disagree. Applicants have amended Claim 1 to recite that the high specificity cytokine antagonist is an inhibitor of TNF-α synthesis. Claims 36, 39-43, 45, 58,

60, 61 and 63-65 depend upon Claim 1, and, therefore, contain the same limitation. Thus, Applicants' invention is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis.

None of the references cited by the Examiner alone or in combination teach or suggest treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis. As discussed above, Lehman *et al.* does not teach or suggest administration via trans-capsular injection. Further, Lehman *et al.* does not teach or suggest treating an inflamed orthopedic joint with an inhibitor of TNF-α synthesis. In fact, Lehman *et al.* teaches away from administration of an inhibitor of TNF-α synthesis in favor of a substance known to have at least some stimulatory effects on TNF-α activity (thalidomide). Thus, Lehman *et al.* does not describe or suggest Applicants' invention, and does not provide a reasonable expectation of successfully treating an inflamed orthopedic joint by trans-capsularly administering into the joint space an inhibitor of TNF-α synthesis.

Pike *et al.* disclose the treatment of articular cartilage disorders by administering IGF-1, a growth factor. Such treatment includes administering IGF-1 by, for example, intra-articular injection. Pike *et al.* does not teach or suggest administering an inhibitor of TNF-α synthesis. Thus, Pike *et al.* does not describe or suggest Applicants' invention, and does not provide a reasonable expectation of treating an inflamed orthopedic joint by trans-capsularly administering an inhibitor of TNF-α synthesis.

One of ordinary skill in the art would not be motivated to combine the teachings of Lehman *et al.* and Pike *et al.* with any reasonable expectation of success in practicingf Applicants' claimed methods of treating an inflamed orthopedic joint by administering an inhibitor of TNF-α synthesis. Thus, none of the Examiner's cited references alone or in combination teach or suggest treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis.

In view of the above, Applicants' claims meet the requirements of 35 U.S.C. § 103(a). Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection to Claim 50 Under 35 U.S.C. § 103(a)

Claim 50 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Lehman Lehman *et al.*, "Thalidomide Therapy for Recalcitrant Systemic Onset Juvenile Rheumatoid Arthritis," *The Journal of Pediatrics, 140*:125-127 (2002) in view of Pike *et al.* (US Publication No. 20030134792, published July 17, 2003) and Molloy *et al.* "The Roles of Growth Factors in Tendon and Ligament Healing," *Sports Med., 33*:381-394 (2003). The Examiner states that "[i]t would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify a formulation comprising thalidomide, as taught by Lehman by adding a growth factor such as PDGF as suggested by Pike et al. and Molloy et al."

Applicants respectfully disagree. Applicants' invention is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis. Applicants have amended Claim 1 to recite that the high specificity cytokine antagonist is an inhibitor of TNF-α synthesis. Claim 50 depends upon Claim 1, and, therefore, contains the same limitation. Claim 50 recites "wherein the growth factor is provided by platelet concentrate."

None of the references cited by the Examiner alone or in combination teach or suggest treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis. For the reasons discussed above, and for the fact that Lehman *et al.* and Pike *et al.* do not teach or suggest providing the growth factor by platelet concentrate, Lehman *et al.* and Pike *et al.* do not alone or in combination teach or suggest Applicants' invention.

Molloy *et al.* teaches that PDGF plays a role in tendon healing. Molloy *et al.* does not teach or suggest Applicants' claimed methods of trans-capsular administration. Molloy *et al.* does not teach or suggest administering an inhibitor of TNF-α synthesis. Thus, Molloy *et al.* does not describe or suggest Applicants' invention, does not provide a reasonable expectation of treating an inflamed orthopedic joint by trans-capsularly administering into the joint space an inhibitor of TNF-α synthesis.

One of ordinary skill in the art would not be motivated to combine the teachings of Lehman *et al.*, Pike *et al.* and Molloy *et al.* with any reasonable expectation of success in treating an inflamed orthopedic joint, as claimed by Applicants. Thus, none of the references cited by the

Examiner alone or in combination teach or suggest treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis.

In view of the above, Applicants' claims meet the requirements of 35 U.S.C. § 103(a). Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection to Claims 53 and 57 Under 35 U.S.C. § 103(a)

Claims 53 and 57 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Lehman *et al.*, "Thalidomide Therapy for Recalcitrant Systemic Onset Juvenile Rheumatoid Arthritis," *The Journal of Pediatrics, 140*:125-127 (2002) in view of Smith *et al.* (U.S. Publication No. 20020169162, published November 14, 2002). The Examiner states that "[i]t would have been obvious to the person of ordinary skill in the art at the time the invention was made to administer a formulation comprising thalidomide as taught by Lehman et al. using the pump device disclosed by Smith et al."

Applicants respectfully disagree. Applicants' invention is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis. Applicants have amended Claim 1 to recite that the high specificity cytokine antagonist is an inhibitor of TNF-α synthesis. Claims 53 and 57 depend upon Claim 1, and, therefore, contain the same limitation. Claim 53 is directed to injecting the inhibitor of TNF-α synthesis into the synovial fluid. Claim 57 is directed to administering the inhibitor of TNF-α synthesis through a drug pump.

None of the Examiner's cited references alone or in combination teach or suggest treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis. As discussed above, Lehman *et al.* teaches systemic administration of thalidomide. Lehman *et al.* does not teach or suggest trans-capsularly administering an inhibitor of TNF-α synthesis in the synovial fluid-containing portion of the joint. Further, Lehman *et al.* does not teach or suggest administering an inhibitor of TNF-α synthesis through a drug pump. Thus, Lehman *et al.* does not teach or suggest Applicants' claimed invention.

Smith *et al.* teaches surgically implanting intraarticularly, i.e., within the synovial joint, a sustained release device. (See Smith *et al.* at paragraph 0046). According to Smith *et al.*, the sustained release device is capable of releasing drugs or compounds over an extended period of

time in a controlled fashion, as opposed to repeated injections (See Smith *et al.* at paragraphs 0012 and 0047). Thus, Smith *et al.* teaches away from administration by injection. (See also Smith *et al.* at paragraphs 006-008). Smith *et al.* does not teach or suggest an administering an inhibitor of TNF-α synthesis. Smith *et al.* does not describe or suggest Applicants' invention, and does not provide a reasonable expectation of treating an inflamed orthopedic joint by trans-capsularly administering into the joint space an inhibitor of TNF-α synthesis, either by injection or by drug pump.

One of ordinary skill in the art would not be motivated to combine the teachings of Lehman *et al.* and Smith *et al.* with any reasonable expectation of success in treating an inflamed orthopedic joint, by transcapsular administration of an inhibitor of TNF-α synthesis, as claimed by Applicants. Thus, none of the Examiner cited references alone or in combination teach or suggest Applicants' claimed methods of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis.

In view of the above, Applicants' claims meet the requirements of 35 U.S.C. § 103(a). Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection to Claim 55 Under 35 U.S.C. § 103(a)

Claim 55 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Lehman *et al.*, "Thalidomide Therapy for Recalcitrant Systemic Onset Juvenile Rheumatoid Arthritis," *The Journal of Pediatrics, 140*:125-127 (2002) in view of Cardone *et al.*, "Diagnostic and Therapeutic Injection of Hip and Knee," *American Family Physician, 67*:2147-2152 (2003). The Examiner states that "[i]t would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of administration of thalidomide as taught by Lehman et al. by aspirating fluid from the knee just prior to administration as suggested by Cardone et al."

Applicants respectfully disagree. Applicants have amended Claim 1 to recite that the high specificity cytokine antagonist is an inhibitor of TNF-α synthesis. Claim 55 depends upon Claim 1, and, therefore, contains the same limitation. Claim 55 is directed to removing a portion of the synovial fluid prior to administration of the inhibitor of TNF-α synthesis. Thus,

Applicants invention is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis.

None of the references cited by the Examiner alone or in combination teach or suggest treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis. As discussed above, Lehman *et al.* does not teach or suggest Applicants' invention.

Cardone *et al.* teaches injection procedures and aspiration procedures for the knee. Cardone *et al.* does not teach or suggest removing a portion of the synovial fluid prior to trans-capsular administration of an inhibitor of TNF-α synthesis. Thus, Cardone *et al.* does not describe or suggest Applicants' invention, does not provide a reasonable expectation of treating an inflamed orthopedic joint by trans-capsularly administering into the joint space an inhibitor of TNF-α synthesis.

One of ordinary skill in the art would not be motivated to combine the teachings of Lehman *et al.* and Cardone *et al.* with any reasonable expectation of success in treating an inflamed orthopedic joint, by the methods claimed by Applicants. Thus, none of the Examiner's cited references alone or in combination teach or suggest treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis.

In view of the above, Applicants' claims meet the requirements of 35 U.S.C. § 103(a). Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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Dated: April 4, 2006